

What is Claimed is:

1. A freeze-drying process, comprising:
 - providing input data representative of a container holding a portion of a product comprising water;
 - loading the container onto a shelf within a drying chamber of a freeze-drying apparatus;
 - freezing at least some of the product water;
 - calculating an initial product temperature based on the input data;
 - calculating a target chamber pressure based on the target product temperature;
 - beginning a primary drying stage, comprising,
 - lowering pressure within the drying chamber to the target chamber pressure;
 - adjusting the shelf to the initial product temperature;
 - removing a majority of the frozen water by sublimation;
 - generating a signal based on a condition of the product;
 - receiving the generated signal;
 - calculating a target product temperature as a function of the generated signal; and
 - adjusting the shelf to the target product temperature.
2. The method of claim 1 wherein the generated signal comprises manometric temperature measurement data.
3. The method of claim 1 comprising the steps of:
 - generating a plurality of signals each based on a condition of the product at a respective plurality of times during the primary drying stage;
 - receiving each generated signal sequentially;
 - calculating a plurality of target product temperatures as a function of each of the generated signals in the plurality; and
 - adjusting the shelf toward each target product temperature in the plurality.
4. The method of claim 1 wherein the generated signal comprises pressure within the drying chamber measured at a plurality of times during the primary drying stage.

5. The method of claim 1 wherein the step of generating a signal comprises measuring pressure independent of gas composition within the drying chamber over a time period.
6. The method of claim 1 comprising the steps of:
 - generating a plurality of signals each based on a condition of the product at a respective plurality of times during the primary drying stage;
 - receiving each generated signal sequentially;
 - calculating a plurality of target product temperatures as a function of each of the generated signals in the plurality;
 - adjusting the shelf to each target product temperature in the plurality; and
 - recording each time and respective target product temperature.
7. The method of claim 1 comprising the steps of:
 - generating a plurality of signals each based on a condition of the product at a respective plurality of times during the primary drying stage;
 - receiving each generated signal sequentially;
 - calculating a plurality of target product temperatures as a function of each of the generated signals in the plurality;
 - adjusting the shelf to each target product temperature in the plurality;
 - storing each time and respective target product temperature; and
 - using the stored time and product temperature to adjust the shelf temperature of a different primary drying stage comprising a different portion of the product.
8. The method of claim 1 wherein the step of generating a signal comprises measuring pressure within the drying chamber independent of atmosphere composition within the drying chamber and over a time period and wherein the product condition comprises at least one of product temperature at the sublimation interface and resistance of previously dried product to water vapor flow.
9. The method of claim 1, wherein:
 - the freeze drying apparatus comprises a condenser chamber fluidly connected to the drying chamber; a valve selectively isolating the drying chamber from the condenser chamber; a differential capacitance manometer pressure sensor fluidly connected to measure pressure in

the drying chamber; a vacuum source fluidly connected to the condenser chamber; means for control of the shelf temperature; and a controller operably connected to the valve, the differential capacitance manometer pressure sensor and the means for control of the shelf temperature;

the step of providing input data comprises providing input data to the controller;

the steps of calculating an initial product temperature and a target chamber pressure are performed by the controller;

the steps of lowering pressure within the drying chamber and adjusting the shelf to the initial product temperature are controlled by the controller;

the step of generating a signal comprises,

sending a first valve control signal from the controller to the valve,

receiving the first valve control signal and closing the valve thereby fluidly isolating the drying chamber from the condenser chamber,

measuring a pressure within the isolated drying chamber using the differential capacitance manometer pressure sensor,

generating a signal that is representative of the measured pressure;

sending a second valve control signal from the controller to the valve,

receiving the second valve control signal and opening the valve thereby fluidly connecting the drying chamber to the condenser chamber,

the step of receiving the generated signal comprises receiving the generated signal at the controller;

the step of calculating a target product temperature is performed by the controller; and

the step of adjusting the shelf to the target product temperature comprises,

sending a first shelf temperature control signal from the controller to the means for control of the shelf temperature, and

receiving the first shelf temperature control signal and adjusting the shelf temperature toward the target product temperature as a result thereof.

10. A freeze-drying apparatus, comprising;

a drying chamber having a shelf for supporting a container holding a portion of a product;

means for admitting an inert gas within the drying chamber;

means for adjusting temperature of the shelf;

a differential capacitance manometer pressure sensor fluidly connected to measure pressure in the drying chamber and provide a signal representative of the measured pressure;

a condenser chamber fluidly connected to the drying chamber;
a vacuum source fluidly connected to the condenser chamber; and
a microprocessor controller for receiving the signal, calculating a product condition as a function of the signal, generating a control signal as a function of the calculated product condition and modulating the shelf temperature and drying chamber pressure using the control signal.

11. The apparatus of claim 10 comprising digital storage means for storing the control signal.

12. The apparatus of claim 10 wherein the signal comprises pressure rise within the drying chamber over a time period and wherein the calculated product condition comprises at least one of product temperature at a sublimation interface and resistance of previously dried product to water vapor flow.

13. The apparatus of claim 10 wherein the signal comprises manometric temperature measurement data and wherein the calculated product condition comprises at least one of product temperature at a sublimation interface and resistance of previously dried product to water vapor flow.

14. A method of sublimating water from a product, comprising:

stage I:

- step 1) loading at least one vial filled with a portion of a product comprising water into a freeze dryer;
- step 2) recording data, including number of vials (N), inner area of vials (A_p in cm^2), fill depth of vials (L in cm), fill weight of vials (W in g) and effective chamber volume (V in liter);
- step 3) recording data, including concentration of solution (C in g/g) and one of collapse temperature (T_c in $^{\circ}\text{C}$), glass transition temperature (T_g' in $^{\circ}\text{C}$) or eutectic temperature (T_{eu} in $^{\circ}\text{C}$);
- step 4) going to stage II freezing;

stage II freezing:

freezing some of the water in the product using one of II a or II b:

II a, for formulation with crystalline products and/or crystalline bulking agents:

- step 1) cooling the shelf at a rate of about 1°C/min to about 5°C, holding for about 30 min;
- step 2) cooling the shelf at a rate of about 1°C/min to about -5°C, holding for about 30 min;
- step 3) cooling the shelf at a rate of about 1°C/min to about -30°C;
- step 4) heating the shelf at a rate of about 1°C/min to about -22°C, holding for about 180 min;
- step 5) cooling the shelf at a rate of about 1°C/min to the lower temperature of $T_c - 5^\circ\text{C}$ or -40°C ;
- step 6) holding the shelf temperature at the stage II, step 5 temperature for 60 min if the fill depth <1 cm, or holding the shelf temperature at the stage II, step 5 temperature for 120 min if the fill depth >1 cm.
- step 7) go to stage III Primary drying - initial; or

II b for formulation without crystalline products or bulking agents (amorphous only):

- step 1) cooling the shelf at a rate of about 1°C/min to about 5°C, holding for about 30 min;
- step 2) cooling the shelf at a rate of about 1°C/min to about -5°C, holding for about 30 min;
- step 3) cooling the shelf at a rate of about 1°C/min to the lower temperature of $T_g' - 5^\circ\text{C}$ or -40°C ;
- step 4) holding the shelf temperature at the stage II, step 3 temperature for 60 min if the fill depth <1 cm; or holding the shelf temperature at the stage II, step 3 temperature for 120 min if the fill depth >1 cm;
- step 5) going to stage III Primary drying - initial;

stage III Primary drying - initial:

determining the initial shelf temperature (T_s) using one of III a or III b:

III a

- step 1) calculating a drying chamber pressure (P_c) by **equation 1**;
- step 2) setting the drying chamber pressure to the value of P_c calculated in stage III a, step 1;
- step 3) calculating an estimated initial product temperature $T_p(\text{initial})$ by **equation 1.2**;
- step 4) setting the shelf temperature to $T_p(\text{initial})$ calculated in stage III a, step 3;
- step 5) going to stage IV primary drying; or

III b

- step 1) calculating a chamber pressure (P_c) by **equation 1**;
- step 2) setting the chamber pressure to P_c calculated immediately above in stage III b, step 1;
- step 3) calculating a heat transfer coefficient (K_v) by **equation 12**;
- step 4) calculating an ice vapor pressure (P_{ice}) by **equation 14**;
- step 5) assigning a value to R_p , wherein
 - if concentration of solution $C \leq 1\%$, then $R_p=2$,
 - if concentration of solution $1\% < C < 10\%$, then $R_p=4$,
 - if concentration of solution $C \geq 10\%$, then $R_p=6$;
- step 6) calculating a total heat flow ($dQ/dt \text{ total}$) by **equation 16**, wherein if $dQ/dt \text{ (total)} > Q_{of}$, then $dQ/dt \text{ (total)} = Q_{of}$;
- step 7) calculating a value for dm/dt by **equation 17**;
- step 8) calculating a value for $T_s(\text{initial})$ by **equation 13**;
- step 9) adjusting the shelf temperature to the $T_s(\text{initial})$ value calculated in stage III b, step 8 at a rate of about 0.5°C/min ;
- step 10) collecting MTM data every 15 min;
- step 11) assigning an ice thickness: $L' = L/0.918$, where L is the liquid fill depth;
- step 12) fitting the MTM data collected in stage III b, step 10 to **equation 2** to yield P_{ice} and R_p ;
- step 13) calculating a value for $T_p \text{ MTM}$ by **equation 3**, wherein if $T_p \text{ MTM} >$

$T_p(\text{initial})$, then decrease shelf temperature 5 °C at the maximum cooling rate, this new shelf temperature then becomes $T_s(\text{initial})$, the initial target product temperature, $T_p(\text{initial})$, is T_c - a safety margin, the safety margin is initially 3°C, the safety margin is re-calculated once the first MTM measurement is made and the target product temperature, T_p , is re-evaluated;

step 14) going to stage IV primary drying;

stage IV primary drying:

- step 1) equilibrating the shelf temperature to within 2°C of T_s initial for 60 min;
- step 2) collecting MTM data every 30 min;
- step 3) assigning an ice thickness as $L' = L/0.918$, where L is the liquid fill depth;
- step 4) fitting MTM data to **equation 2** to yield P_{ice} and R_p ;
- step 5) calculating a value for T_p MTM by **equation 3**;
- step 6) calculating a value for mass flow (dm/dt) by **equation 4**;
- step 7) calculating a value for nominal heat flow $(dQ/dt)_{MTA-1}$ by **equation 5**, wherein if $(dQ/dt)_{MTA-1} \geq Q_{of}$, then $(dQ/dt)_{MTA-1} = Q_{of}$, else $(dQ/dt)_{MTA-1}$ is the value calculated from **equation 5**;
- step 8) calculating a value for product temperature $T_{p\text{overflow}}$ by **equation 15**;
- step 9) calculating a value for primary drying time, t_{primary} , by **equation 6**;
- step 10) estimating a value for $T_p(\text{target})$ product temperature, wherein
 - if $t_{\text{primary}} < 6$ hr; use 5°C safety margin ($T_p(\text{target}) = T_c - 5^\circ \text{C}$),
 - if $t_{\text{primary}} > 48$ hr; use 2°C safety margin ($T_p(\text{target}) = T_c - 2^\circ \text{C}$),
 - else use 3°C safety margin ($T_p(\text{target}) = T_c - 3^\circ \text{C}$),
 - if $T_p(\text{target}) \geq T_{p\text{overflow}}$, then $T_p(\text{target}) = T_{p\text{overflow}}$;
- step 11) calculating a value for shelf temperature (T_s) using **Method 1**:

Method 1:

calculating temperature of bottom ice (T_b) by **equation 10**;
 calculating heat transfer coefficient of vials (K_v) by **equation 11**;
 calculating a value for the shelf temperature (T_s) by **equation 7** and setting the shelf temperature to this calculated T_s value;

- step 12) calculating a value for chamber pressure (P_c) by **equation 1** using target product temperature as evaluated above using the safety margin selected based upon the primary drying time;
- step 13) adjusting the chamber pressure to P_c calculated in stage IV, step 12;
- step 14) collecting MTM data at time intervals;
- step 15) fitting the MTM data to **equation 2** to yield P_{ice} and R_p ;
- step 16) calculating a value for T_p MTM by **equation 3**;
- step 17) calculating a value for nominal heat flow by **equation 5**;
- step 18) calculating a value for ice thickness using **Method 2**:

Method 2

- calculating a value for mass flow by **equation 4**;
- calculating a value for total weight of ice sublimed ($W_{\text{sublimation}}$) by **equation 8**;
- calculating a value for ice thickness (L_{ice}) by **equation 9**;
- step 19) calculating a value for the shelf temperature (T_s) using **Method 1**;

Method 1:

- calculating the temperature of bottom ice (T_b) by **equation 10**;
- calculating a value for the heat transfer coefficient of vials (K_v) by **equation 11**;
- calculating a value for shelf temperature (T_s) by **equation 7**;
- step 20) adjusting the shelf temperature to T_s calculated in stage IV, step 19 at a rate of about 1 °C/min;
- step 21) collecting MTM data every 15 minutes and fitting the MTM data to **equation 2** to yield P_{ice} and R_p ;
- step 22) calculating a value for T_p MTM by **equation 3**, wherein if $T_p \text{ MTM} > T_p(\text{target}) + 1^\circ\text{C}$, then calculate T_s by **equation 7** and adjust the shelf temperature to this calculated T_s (stage IV, step 22), else leave the shelf temperature at T_s calculated in stage IV, step 19;
- step 23) going to stage IV, step 24 after the shelf temperature stabilizes at the T_s chosen in stage IV, step 22 for 1 hour or longer;

- step 24) collecting MTM data every 60 min;
- step 25) fitting the MTM data generated in stage IV, step 24 to **equation 2** to yield P_{ice} and R_p , wherein

If $P_{ice} > P_0 + 5 \text{ mTorr}$, go to **Method 4**,

Method 4,

- calculating a value for T_p MTM by **equation 3**;
- calculating a value for nominal heat flow by **equation 5**;
- calculating a value for ice thickness by using **Method 3**,

Method 3,

- calculating a value for mass flow by **equation 4**,
- calculating a value for total weight of ice sublimation ($W_{\text{sublimation}}$) by **equation 8**,
- calculating a value for ice thickness (L_{ice}) by **equation 9**, wherein, if $L_{ice} > (1/3) * (L/0.918)$ and $T_p < T_p(\text{target}) - 1^\circ\text{C}$ or $T_p > T_p(\text{target}) + 1^\circ\text{C}$, then calculate T_s by **Method 1** as described in Section IV, step 17, and adjust the shelf temperature to this value of T_s , (here, T_p means T_p MTM or product temperature evaluated experimentally by temperature sensors (i.e., thermocouples) placed directly in several vials, whichever method of temperature measurement is being employed; if $L_{ice} \leq (1/3) * (L/0.918)$ leave the shelf temperature at T_s previously calculated in stage IV, step 19; (note: if the ice remaining is so small as to meet this criterion, primary drying is almost over, and the shelf temperature is left where it was until primary drying is fully over);
- If $P_{ice} \leq P_0 + 5 \text{ mTorr}$ for one MTM measurements, go to stage IV, step 24; If $P_{ice} \leq P_0 + 5 \text{ mTorr}$ for two successive MTM measurements, go to stage 5, secondary drying.

15. The method of claim 14 wherein stage 5, secondary drying comprises one of V a or V b:

V a For formulation with crystalline products and/or crystalline bulking agents:

- step 1) adjusting the shelf temperature to about 40 °C at a rate of about 0.3°C/min;
- step 2) holding the shelf temperature at about 40 °C for about 60 minutes;
- step 3) adjusting the shelf temperature to about 50 °C at a rate of about 0.3°C/min;
- step 4) maintaining the shelf temperature at about 50 °C for about 180 min; and
- step 5) adjusting the shelf temperature to 25°C at a rate of about 2°C/min; or

V a For non-crystalline formulations:

- step 1) adjusting the shelf temperature to about 40 °C at a rate of about 0.1°C/min;
- step 2) maintaining the shelf temperature at about 40 °C for about 240 min (if the concentration of formulation $\leq 5\%$ w/w); or maintaining the shelf temperature at about 40 °C for about 360 min (if the concentration of formulation $> 5\%$ w/w); and
- step 3) adjusting the shelf temperature to about 25°C at a rate of about 2°C/min; or

V b:

- step 1) determining the residual moisture content of some of the product;
- step 2) closing a valve separating the drying chamber from a condenser chamber and accumulating the pressure vs. time data;
- step 3) calculating the weight percent residual moisture using equations 18, 19, and 20.
- step 4) adjusting the shelf temperature to about 40°C and holding the shelf temperature at 40 °C for about 60 minutes;
- step 5) repeating steps 2-4 at hourly intervals until either: (a) the calculated residual moisture is less than or equal to the target residual moisture or (b) the total time elapsed since the beginning of this step exceeds 4 hours, if (a) is true, go to step 7 below; if (b) is true, go to step 6 below;
- step 6) adjusting the shelf temperature to about 50°C; holding the shelf temperature at about 50 °C for about 60 minutes, and repeating steps 1-4 at hourly intervals until either the calculated residual moisture is less than or equal to the target

residual moisture or the total time elapsed in this step exceeds four hours, go to step 7; and
step 7). adjusting the shelf temperature to about 25°C at a rate of about 2°C/min.

16. The method of claim 14 comprising:
providing a controller having digital storage means; and
saving parameters from the method, including optimized chamber pressure, target product temperature and shelf temperature vs. time profile to the digital storage means.